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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/850,041	05/07/2001	Attila Lorincz	2629-4023	1436

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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 12/17/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/850,041	Applicant(s) LORINCZ ET AL.	
	Examiner Carla Myers	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Claims 28-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-32 are indefinite over the recitation of "the antibody or antibody fragment" because this phrase lacks proper antecedent basis. While the claim previously refers to a "functional anti-hybrid fragment", the claim does not previously refer to an "antibody fragment". This rejection may be overcome by amendment of the claims to recite "functional anti-hybrid antibody fragment".

Claims 28-32 are indefinite for failing to recite a final process step which agrees back with the preamble. The claims are drawn to a method for detecting a target nucleic acid sequence. However, the claims recite a final step of detecting a bound hybrid. Therefore it is not clear as to whether the claims are intended to be limited to methods for detecting target nucleic acid sequences or methods for detecting bound hybrids. This rejection may be overcome by amendment of the claims to recite that detection of the bound hybrid is indicative of the presence of the target nucleic acid sequence.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,228,578. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '578 are both drawn to non-radioactive hybridization assays which comprise the steps of hybridizing a nucleic acid that has been hydrolyzed with base to a probe to form a double-stranded DNA/RNA hybrid; capturing the hybrid onto a solid phase to which an anti-RNA/DNA antibody has been immobilized; eliminating non-hybridized probe, particularly by nuclease digestion; and detecting bound DNA/RNA hybrids. Furthermore, the instant claims and the claims of '578 are both inclusive of kits comprising a transport medium, a probe, a solid phase to which an anti-RNA/DNA antibody is immobilized and a means for detecting DNA/RNA hybrids.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Dattagupta (U.S. Patent No. 4,968,602) .

Dattagupta (column 2) teaches a non-radioactive hybridization assay comprising (a) denaturing a target DNA with sodium hydroxide (column 17, lines 3-6); (b) hybridizing a RNA

probe to the target DNA to form a double-stranded RNA/DNA hybrid; (c) capturing the hybrid onto a solid phase using an immobilized antibody specific for the hybrid (column 8, lines 57-61); (d) removing unhybridized probe; and (e) detecting the bound hybrid (column 19, lines 5-8). Dattagupta (column 24, lines 45-66) teaches lysing cells in the sample and denaturing the target DNA with 0.2N NaOH at 80°C for a "determined length of time". Dattagupta (column 17, lines 21-37) also teaches using a buffer to restore the pH to neutrality following denaturation, in order to allow for the hybridization of the RNA probe to the target DNA. The reference also teaches a number of examples of non-radioactive labels that can be used to detect the double-stranded RNA/DNA hybrid. Furthermore, Dattagupta (columns 17 and 18) discloses packaging the reagents necessary to perform the hybridization assay into a kit. Dattagupta generically describes the components of the kit as including "hybridization solution", "denaturation agents" and "all configurations and compositions for performing the various hybridization formats described". However, it is a characteristic of the kit of Dattagupta that it includes a solution in which the biological sample is "stabilized", an RNA probe, a solid support to which an anti-RNA/DNA antibody has been immobilized and a means to detect double-stranded hybrid because each of these compositions are disclosed in the assay formats taught by Dattagupta. Accordingly, claims 28 and 33 are anticipated by the disclosure of Dattagupta.

4. Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by Rashtchian (Clinical Chemistry (1987) 33: 1526-1530).

Rashtchian (page 1527) teaches a non-radioactive hybridization assay comprising (a) treating a cell sample with sodium hydroxide lysis solution to generate a "hydrolyzed sample of cells"; (b) contacting the hydrolyzed sample of cells with a DNA probe to form a double-stranded RNA/DNA hybrid between the DNA probe and target RNA; c) capturing the RNA/DNA hybrid onto a solid phase using an immobilized antibody specific for the hybrid; (d) washing to remove unhybridized probe; and (e) detecting the bound hybrid as indicative of the presence of the target RNA.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rashtchian.

Rashtchian (page 1527) teaches a non-radioactive hybridization assay comprising (a) treating a cell sample with sodium hydroxide lysis solution to generate a "hydrolyzed sample of cells"; (b)

contacting the hydrolyzed sample of cells with a DNA probe to form a double-stranded RNA/DNA hybrid between the DNA probe and target RNA; c) capturing the RNA/DNA hybrid onto a solid phase using an immobilized antibody specific for the hybrid; (d) washing to remove unhybridized probe; and (e) detecting the bound hybrid as indicative of the presence of the target RNA. The bound hybrids are detected using a streptavidin-peroxidase reagent. The method of Rashtchian requires the use of the reagents of buffers, which can be used to stabilize biological samples, a DNA probe, a solid support to which an anti-RNA/DNA antibody has been immobilized, and a streptavidin-peroxidase reagent for detecting bound RNA/DNA hybrids. Rashtchian does not teach packaging these reagents into a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents of a buffer, a DNA probe, a solid-support having an anti-RNA/DNA antibody immobilized thereon, and a detection means in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to perform the detection method of Rashtchian.

6. Claims 28-33 are rejected under 35 U.S.C. § 103 as being unpatentable over Dattagupta in view of Thompson.

Dattagupta (column 2) teaches a non-radioactive hybridization assay comprising (a) denaturing a target DNA with sodium hydroxide (column 17, lines 3-6); (b) hybridizing a RNA probe to the target DNA to form a double-stranded RNA/DNA hybrid; (c) capturing the hybrid onto

a solid phase using an immobilized antibody specific for the hybrid (column 8, lines 57-61); (d) removing unhybridized probe; and (e) detecting the bound hybrid (column 19, lines 5-8). Kits are also disclosed comprising the reagents necessary to perform the non-radioactive hybridization assay (columns 17 and 18). Dattagupta (column 24, lines 45-66) teaches lysing cells in the sample and denaturing the target DNA with 0.2N NaOH at 80°C for a determined length of time. Specifically, Dattagupta (col. 17) teaches that following denaturation and fragmentation of the sample nucleic acid with NaOH, the sample can then be utilized in nucleic acid hybridization assays, which involve the hybridization of a probe to the sample nucleic acid to form a double-stranded hybrid. Dattagupta teaches removing unhybridized probe by performing repeated wash steps but does not teach using an enzyme, such as RNase, to remove unhybridized probe.

However, Thompson et al. (p. 264, column 2) discloses a hybridization assay wherein unhybridized RNA probe is removed from the reaction mixture by treatment with RNase. Thompson (p. 264) states that "in solution hybridization, unreacted probe is usually in vast excess over hybrids. This creates the problem of a background signal arising from non-specific interaction of probe with solid supports used to purify hybrids. Background signals usually determine the sensitivity of an assay. Three general strategies have been employed to accomplish hybrid purification: selective immobilization, nuclease digestion of unhybridized probe, and sandwich hybridization". In view of the disclosure of Thompson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Dattagupta so as to have included the step of RNase digestion taught by Thompson for the advantage expressly stated by Thompson of more

efficiently removing unhybridized probe, thereby reducing background signal and increasing the overall sensitivity of the detection method.

Secondly, Dattagupta does not teach using a specific concentration of probe. However, to determine the optimum concentration of reactants is well within the skill of the art (see In re Kronig 190 U.S.P.Q. 425). Furthermore, Thompson (page 264) teaches that solution hybridization methods should be performed using excess probe. As stated by Thompson, "under these conditions, all targets in a sample can be saturated with probe. The rate of the reaction is dependent upon the concentration of probe, and independent of target concentration, so that all reactions are complete at the same time, regardless of the amount of target present". Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and well within the skill of the art to have selected and used an effective amount of probe based upon the specific reaction conditions for each sample for the expected benefit of optimizing the effectiveness and sensitivity of the non-radioactive hybridization method.

7. Claims 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rashtchian in view of Thompson.

Rashtchian (page 1527) teaches a non-radioactive hybridization assay comprising (a) treating a cell sample with sodium hydroxide lysis solution to generate a "hydrolyzed sample of cells"; (b) contacting the hydrolyzed sample of cells with a DNA probe to form a double-stranded RNA/DNA hybrid between the DNA probe and target RNA; c) capturing the RNA/DNA hybrid onto a solid phase using an immobilized antibody specific for the hybrid; (d) washing to remove unhybridized

probe; and (e) detecting the bound hybrid as indicative of the presence of the target RNA. Rashtchian teaches removing unhybridized probe by performing repeated wash steps but does not teach using an enzyme, such as RNase, to remove unhybridized probe.

However, Thompson et al. (p. 264, column 2) discloses a hybridization assay wherein unhybridized RNA probe is removed from the reaction mixture by treatment with RNase. Thompson (p. 264) states that "in solution hybridization, unreacted probe is usually in vast excess over hybrids. This creates the problem of a background signal arising from non-specific interaction of probe with solid supports used to purify hybrids. Background signals usually determine the sensitivity of an assay. Three general strategies have been employed to accomplish hybrid purification: selective immobilization, nuclease digestion of unhybridized probe, and sandwich hybridization". In view of the disclosure of Thompson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rashtchian so as to have included the step of RNase digestion taught by Thompson for the advantage expressly stated by Thompson of more efficiently removing unhybridized probe, thereby reducing background signal and increasing the overall sensitivity of the detection method.

Secondly, Rashtchian does not teach methods in which 1-500 ng/ml, particularly 75 ng/ml is utilized. However, to determine the optimum concentration of reactants is well within the skill of the art (see In re Kronig 190 U.S.P.Q. 425). Furthermore, Thompson (page 264) teaches that solution hybridization methods should be performed using excess probe. As stated by Thompson, "under these conditions, all targets in a sample can be saturated with probe. The rate of the reaction

is dependent upon the concentration of probe, and independent of target concentration, so that all reactions are complete at the same time, regardless of the amount of target present". Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and well within the skill of the art to have selected and used an effective amount of probe based upon the specific reaction conditions for each sample for the expected benefit of optimizing the effectiveness and sensitivity of the non-radioactive hybridization method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER

December 12, 2001